L8 ANSWER 4 OF 4 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 91046024 MEDLINE
DOCUMENT NUMBER: 91046024 PubMed ID: 2172988
TITLE: Introduction of nerve growth factor (**NGF**) receptors into a medulloblastoma cell line results in expression of high- and low-affinity **NGF** receptors but not **NGF**-mediated differentiation.
AUTHOR: Pleasure S J; Reddy U R; Venkatakrishnan G; Roy A K; Chen J; Ross A H; Trojanowski J Q; Pleasure D E; Lee V M
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1990 Nov) 87 (21) 8496-500. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199012
ENTRY DATE: Entered STN: 19910208
Last Updated on STN: 19970203
Entered Medline: 19901207

AB Expression of the cloned human nerve growth factor receptor (NGFR) cDNA in cell lines can generate both high- and low-affinity binding sites. Since the inability to respond appropriately to differentiation factors such as **NGF** may contribute to determining the malignant phenotype of **neuroblastomas**, we sought to determine whether the same is true of medulloblastomas. To generate a human central nervous system neuronal cell line that would respond to **NGF**, we infected the medulloblastoma cell line D283 MED with a defective **retrovirus** carrying the cDNA coding for the human NGFR. The resultant cells (MED-NGFR) expressed abundant low- and high-affinity NGFRs, and **NGF** treatment induced a rapid transient increase of c-fos mRNA in the NGFR-expressing cells but not in the parent line or in cells infected with virus lacking the cDNA insert. However, the MED-NGFR cells did not internalize the NGFR at high efficiency, nor did they differentiate in response to **NGF**. Three important conclusions emerge from this study: (i) internalization of NGFRs is not necessary for some early rapid transcriptional effects of **NGF**; (ii) an unknown factor(s) that cooperates with the cloned NGFR in allowing high-affinity **NGF** binding is found in a primitive central nervous system cell line; and (iii) NGFRs introduced into and expressed by D283 MED (i.e., MED-NGFR) cells are partially functional but are unable to induce differentiation in these primitive neuron-like tumor cells, implying that high-efficiency receptor-mediated endocytosis of **NGF** and its receptor may be a necessary step in the cascade of events

OCUMENT NUMBER: 120:45928
TITLE: Methods and compositions for gene, tumor, and viral infection therapy and prevention of programmed cell death (apoptosis)
INVENTOR(S): Roizman, Bernard; Chou, Joany
PATENT ASSIGNEE(S): Arch Development Corp., USA
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9319591	A1	19931014	WO 1993-US1801	19930226
W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9337818	A1	19931108	AU 1993-37818	19930226
AU 682463	B2	19971009		
JP 07507997	T2	19950907	JP 1993-517439	19930226
EP 675961	A1	19951011	EP 1993-907093	19930226
EP 675961	B1	20021127		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 6172047	B1	20010109	US 1995-483533	19950607
US 6340673	B1	20020122	US 1999-283471	19990401

PRIORITY APPLN. INFO.:
US 1992-861233 A 19920331
WO 1993-US1801 A 19930226
US 1995-419853 B3 19950411
US 1995-483533 A1 19950607

AB Programmed cell death in neurons is prevented or treated by gene therapy using a nonpathogenic vector contg. the .gamma.134.5 gene of herpes simplex virus type 1 (HSV-1), or by treatment with the expression product of this gene, protein ICP34.5, or its functional equivs. The function of .gamma.134.5 is to protect infected nerve cells from shutoff of protein synthesis and consequent programmed cell death, thereby promoting neuronal survival and virus replication and spreading; .gamma.134.5 and ICP34.5 may thus extend the lifetime of nonregenerating neurons in neurodegenerative diseases. The .gamma.134.5 gene and its product also protect neurons and other cells from environmental stresses which may lead to apoptosis, e.g. UV and **NGF** deprivation. Candidate drugs for extending the viability of cells are screened in **neuroblastoma** cells contg. or lacking the .gamma.134.5 gene by applying such stresses and subsequently measuring the cells' viability. The vector may be HSV-1 or HSV-2 altered by deletion of the ICP4, .alpha.4, or .alpha.0 gene to render it nonpathogenic, an altered **retrovirus**, vaccinia virus, picornavirus, coronavirus, bunyavirus, togavirus, or rhabdovirus, or a multipotent neural cell line. Thus, a mouse cerebellar progenitor cell line was **transduced** with replication-incompetent retroviral vector BAG contg. gene .gamma.134.5, then cocultured with a primary culture of dissocd. neonatal mouse cerebellum cells which were finally injected into newborn mice to prevent neuronal degeneration.

modify reconstitution and **transducibility** of infused marrow. Clinical studies using this approach have now begun.

L4 ANSWER 84 OF 94 MEDLINE DUPLICATE 29
ACCESSION NUMBER: 92046361 MEDLINE
DOCUMENT NUMBER: 92046361 PubMed ID: 1658386
TITLE: Human cytomegalovirus inhibits human immunodeficiency virus
replication in cells productively infected by both viruses.
AUTHOR: Koval V; Clark C; Vaishnav M; Spector S A; Spector D H
CORPORATE SOURCE: Department of Biology, University of California, San Diego,
La Jolla 92093-0116.
CONTRACT NUMBER: AI28270 (NIAID)
GM07313 (NIGMS)
MH45294 (NIMH)
SOURCE: JOURNAL OF VIROLOGY, (1991 Dec) 65 (12) 6969-78.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199112
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 19980206
Entered Medline: 19911226

AB We have been studying the role of human cytomegalovirus (HCMV) as a potential cofactor in human immunodeficiency virus (HIV)-related disease. The clinical relevance of HCMV is highlighted by the fact that it is a principal viral pathogen in patients with AIDS and is known to infect the same cells as HIV. In this study, we focused on the molecular interactions between HIV and HCMV in human fibroblasts and in the human **glioblastoma**/astrocytoma-derived cell line U373 MG, cells which can be productively infected by both viruses. Because these cells are CD4-, we used HIV pseudotyped with a murine amphotropic **retrovirus** as described previously (D. H. Spector, E. Wade, D. A. Wright, V. Koval, C. Clark, D. Jaquish, and S. A. Spector, J. Virol. 64:2298-2308, 1990). Initial studies showed that when cells were preinfected with HIV (Ampho-1B) for 5 days and then superinfected with HCMV, HIV antigen production dropped significantly in the coinfected cells but continued to rise in cells infected with HIV (Ampho-1B) alone. HCMV production, however, was unaffected by the presence of HIV. Further analysis showed that HIV steady-state RNA levels and gag and env protein production were also inhibited in the presence of HCMV. The transcriptional inhibition of HIV was particularly surprising in view of the previous results of several other laboratories as well as our own that HCMV infection stimulates HIV long terminal repeat-chloramphenicol acetyltransferase (LTR-CAT) expression in transient expression assays. To investigate this further, we **transfected** the HIV LTR-CAT construct into either uninfected cells or cells which had been preinfected with HIV. The cells were infected with HCMV 24 h posttransfection and assayed for CAT gene expression at 48 h after HCMV infection. Although there was some stimulation of the LTR-CAT in cells that were dually infected by HIV and HCMV, it was 16-fold less than that in the cells infected only with HCMV. This suggests that in the presence of the HIV infection, the stimulation of the HIV LTR-CAT gene by HCMV is significantly reduced. Experiments with UV-irradiated HCMV and the HCMV DNA polymerase inhibitor ganciclovir showed that HCMV transcription is necessary for the reduction in HIV production to occur; however, replication of the HCMV genome or any events which take place after DNA replication are not necessary. These results, coupled with the observation

that inhibition is usually first seen between 8 and 24 h after HCMV infection, suggest that an HCMV early protein is involved in repression of HIV.

L4 ANSWER 85 OF 94 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:117781 CAPLUS
DOCUMENT NUMBER: 118:117781
TITLE: A rat brain mRNA encoding a transcriptional activator homologous to the DNA binding domain of retroviral integrases
AUTHOR(S): Duilio, Angela; Zambrano, Nicola; Mogavero, Anna Rita; Ammendola, Rosario; Cimino, Filiberto; Russo, Tommaso
CORPORATE SOURCE: II Fac. Med. Chir., Univ. Napoli, Naples, 80131, Italy
SOURCE: Nucleic Acids Research (1991), 19(19), 5269-74
CODEN: NARHAD; ISSN: 0305-1048
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A rat cDNA was isolated (named FE65) hybridizing to an mRNA of about 2300 nucleotides present in rat brain, undetectable in rat liver, and very poorly represented in other tissues. An mRNA of the same size is present in human **neuroblastoma** cells and is absent from other human cell lines. The FE65 cDNA contains an open reading frame (ORF) coding for a polypeptide of 499 amino acids in which 143 residues can be aligned with the DNA-binding domain of the integrases encoded by mammalian immunodeficiency viruses. The remaining part of the FE65 ORF is not homologous with the correspondent regions of the integrases; the first 206 residues of the FE65 ORF show numerous neg. charges and a short sequence not dispensable for the function of the transactivating acidic domain of the jun family transcriptional factors. A plasmid which expresses FE65 amino acids 1-232 fused to the yeast GAL4 DNA-binding domain was co-**transfected** with a plasmid contg. five GAL4-binding sites upstream of a minimal adenovirus promoter controlling the expression of the CAT gene. This expt. showed that the fused protein GAL4-FE65 is able to obtain a 30-40-fold increase of the CAT gene expression compared to the expression obsd. in the presence of the GAL4 DNA-binding domain alone. Two types of FE65 mRNA are present in rat brain, differing only by six nucleotides. It is demonstrated that this is the consequence of a neuron-specific alternative splicing of a six-nucleotide miniexon, which is also present in the human genome, in an intron/exon context very similar to that of the rat FE65 gene.

L4 ANSWER 86 OF 94 MEDLINE DUPLICATE 30
ACCESSION NUMBER: 91046024 MEDLINE
DOCUMENT NUMBER: 91046024 PubMed ID: 2172988
TITLE: Introduction of nerve growth factor (NGF) receptors into a medulloblastoma cell line results in expression of high- and low-affinity NGF receptors but not NGF-mediated differentiation.
AUTHOR: Pleasure S J; Reddy U R; Venkatakrishnan G; Roy A K; Chen J; Ross A H; Trojanowski J Q; Pleasure D E; Lee V M
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1990 Nov) 87 (21) 8496-500.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199012
ENTRY DATE: Entered STN: 19910208

Last Updated on STN: 19970203
Entered Medline: 19901207

AB Expression of t[redacted]cloned human nerve growth fact[redacted]receptor (NGFR) cDNA in cell lines can generate both high- and low-affinity binding sites. Since the inability to respond appropriately to differentiation factors such as NGF may contribute to determining the malignant phenotype of **neuroblastomas**, we sought to determine whether the same is true of medulloblastomas. To generate a human central nervous system neuronal cell line that would respond to NGF, we infected the medulloblastoma cell line D283 MED with a defective **retrovirus** carrying the cDNA coding for the human NGFR. The resultant cells (MED-NGFR) expressed abundant low- and high-affinity NGFRs, and NGF treatment induced a rapid transient increase of c-fos mRNA in the NGFR-expressing cells but not in the parent line or in cells infected with virus lacking the cDNA insert. However, the MED-NGFR cells did not internalize the NGFR at high efficiency, nor did they differentiate in response to NGF. Three important conclusions emerge from this study: (i) internalization of NGFRs is not necessary for some early rapid transcriptional effects of NGF; (ii) an unknown factor(s) that cooperates with the cloned NGFR in allowing high-affinity NGF binding is found in a primitive central nervous system cell line; and (iii) NGFRs introduced into and expressed by D283 MED (i.e., MED-NGFR) cells are partially functional but are unable to induce differentiation in these primitive neuron-like tumor cells, implying that high-efficiency receptor-mediated endocytosis of NGF and its receptor may be a necessary step in the cascade of events leading to NGF-mediated differentiation.

L4 ANSWER 87 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 31
ACCESSION NUMBER: 1989:568631 CAPLUS
DOCUMENT NUMBER: 111:168631
TITLE: Retroviral **transfer** of a human tyrosine hydroxylase cDNA in various cell lines: regulated release of dopamine in mouse anterior pituitary AtT-20 cells
AUTHOR(S): Horellou, Philippe; Guibert, Bernard; Leviel, Vincent; Mallet, Jacques
CORPORATE SOURCE: Lab. Neurobiol. Cell. Mol., Cent. Natl. Rech. Sci., Gif-sur-Yvette, 91198, Fr.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1989), 86(18), 7233-7
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Little is known about the mol. events mediating neurotransmitter release, a crucial step in synaptic transmission. In this paper, the biosynthesis and release of L-.beta.-3,4-dihydroxyphenylalanine (L-DOPA) and dopamine were analyzed in 3 heterologous cell lines after retroviral-mediated gene **transfer** of tyrosine hydroxylase (EC 1.14.16.2), the rate-limiting enzyme in catecholamine synthesis. A recombinant **retrovirus** encoding human tyrosine hydroxylase type I as well as neomycin-resistance gene was used to infect a fibroblast (NIH 3T3), a **neuroblastoma** (NS20 Y), and a neuroendocrine (AtT-20) cell line. After selection in the presence of neomycin and in tyrosine-free medium, high levels of exogenous tyrosine hydroxylase activity were detected in exts. of the 3 cell lines. High-performance liq. chromatog. of cell exts. and culture supernatants confirmed that the three cell lines hydroxylated tyrosine to form L-DOPA and released this metabolite into the culture medium. Interestingly, the

neuroendocrine cell line AtT-20 synthesized not only L-DOPA but also dopamine. Evoked secretion studies established that AtT-20 cells released the transmitter upon depolarization in a regulated, calcium-dependent way.

The implication of this approach for the analyses of neurotransmitter release as well as in the context of degenerative disorders such as Parkinson disease is discussed.

L4 ANSWER 88 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 32
ACCESSION NUMBER: 1989:491588 CAPLUS
DOCUMENT NUMBER: 111:91588
TITLE: Activation of muscle-specific genes in pigment, nerve, fat, liver, and fibroblast cell lines by forced expression of MyoD
AUTHOR(S): Weintraub, Harold; Tapscott, Stephen J.; Davis, Robert L.; Thayer, Mathew J.; Adam, Mohammed A.; Lassar, Andrew B.; Miller, A. Dusty
CORPORATE SOURCE: Fred Hutchinson Cancer Res. Cent., Seattle, WA, 98104, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1989), 86(14), 5434-8
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB MyoD is a master regulatory gene for myogenesis. Under the control of a retroviral long terminal repeat, MyoD was expressed in a variety of differentiated cell types by using either a DNA **transfection** vector or a **retrovirus**. Expression of muscle-specific proteins was obsd. in chicken, human, and rat primary fibroblasts and in differentiated melanoma, **neuroblastoma**, liver, and adipocyte lines. The ability of MyoD to activate muscle genes in a variety of differentiated cell lines suggests that no addnl. tissue-specific factors other than MyoD are needed to activate the downstream program for terminal muscle differentiation or that, if such factors exist, they are themselves activated by MyoD expression.

L4 ANSWER 89 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 33
ACCESSION NUMBER: 1989:474091 CAPLUS
DOCUMENT NUMBER: 111:74091
TITLE: Rapid dot blot quantitation of viral DNA and amplified genes in less than 1,000 human cells
AUTHOR(S): Lion, Thomas; Razvi, Nighet; Hutchinson, Mary Ann; Golomb, Harvey M.; Brownstein, Bernard H.
CORPORATE SOURCE: Jt. Sect. Hematol./Oncol., Univ. Chicago, Chicago, IL, 60637, USA
SOURCE: DNA (1989), 8(5), 361-7
CODEN: DNAADR; ISSN: 0198-0238
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The copy no. of intracellular DNA sequences can be quantitated rapidly with great sensitivity in 100-1,000 cells as starting material. The method applies DNA from lysed cells to a charged nylon membrane that permits successive hybridizations with probes for different genes or DNA sequences. This method was tested with 8 types of human cells, including leukemic cells, and has detected Epstein-Barr virus (DNA virus) in immortalized cells, integrated HTLV-I (RNA **retrovirus**) in infected cells, and detd. copy nos. of the amplified multiple

drug-resistance gene in human cells resistant to various cytotoxic agents.
It could also be used for estg. copy no. of **transfected** DNA in human or other mammalian cells. The described method is not as sensitive as polymerase chain reaction may potentially prove, but is easily quantitated for accurate clin. diagnosis where sensitive and quant. assays must be carried out on a limited no. of cells. Examples of the method's clin. application are the staging of human **neuroblastomas** and the evaluation of oncogene amplification, which has prognostic value for both overall survival and relapse time in breast cancer patients.

L4 ANSWER 90 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 34
ACCESSION NUMBER: 1989:630340 CAPLUS
DOCUMENT NUMBER: 111:230340
TITLE: A novel experimental approach to immunotherapy against malignant brain tumor with mouse IFN-.gamma. gene **transfer**
AUTHOR(S): Nishihara, Kiyoshi
CORPORATE SOURCE: Fac. Med., Kyoto Univ., Kyoto, 606, Japan
SOURCE: Archiv fuer Japanische Chirurgie (1989), 58(1), 18-42
CODEN: NIGHAE; ISSN: 0003-9152
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB To investigate the effect of interferon-.gamma. (IFN-.gamma.) on immunotherapy, the autocrine stimulated system in which a mouse IFN-.gamma. cDNA was **transferred** by infection with a chimeric **retrovirus** contg. the IFN-.gamma. gene was used. A tumor-specific CTL clone (E-4) against 203-glioma cells (a 20-methylcholanthrene-induced mouse ependymoblastoma line of C57BL/6 mouse origin) was established, and the murine IFN-.gamma. cDNA was **transferred** into E-4 by using a retroviral vector (pSVX(Mu .gamma. .DELTA.A)). Out of 5 gene-**transferred** subclones, E.gamma.-4, E.gamma.-5, E.gamma.-6, E.gamma.-7 and E.gamma.-9, 2 subclones (E.gamma.-6 and E.gamma.-9) constitutively produced 8- and 10-fold amts. of IFN-.gamma. as compared with the parental E-4. These 2 subclones exhibited 2-3 times higher killing activity against 203-glioma than the parental cells. Enhancement of the killing activities was abrogated by addn. of anti-IFN-.gamma. antibody. The results indicate that the IFN-.gamma. gene **transfer** system could be used as a novel therapeutical approach to tumors; survival times of tumor-bearing mice were prolonged by the active immunization of **neuroblastoma** cells before the tumor transplantation. **Retrovirus**-mediated **transfer** of cytokine genes may be applied to a modified immunotherapy for cancer in the future.

L4 ANSWER 91 OF 94 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:172483 CAPLUS
DOCUMENT NUMBER: 100:172483
TITLE: Chromosomal aberrations and **retrovirus**-like particles produced by in vivo transplantation in neoplastic brain cells of a Drosophila mutant strain
AUTHOR(S): Ryo, Haruko; Shiba, Tadayoshi; Fukunaga, Akihiro; Kondo, Sohei; Gateff, Elisabeth
CORPORATE SOURCE: Fac. Med., Osaka Univ., Osaka, 530, Japan
SOURCE: Gann (1984), 75(1), 22-8
CODEN: GANNA2; ISSN: 0016-450X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The recessive mutation lethal(2) giant larva4 (l(2)gl4) of D. melanogaster causes the development of malignant tumors in the whole brain of homozygous larvae. A mutant brain fragment implanted into the abdomen of a wild-type adult female kills the host in .apprx.10 days. Neuroblasts in

situ in l(2)gl4 larvae showed normal karyotypes, but, when cultured in adult abdomens for 1 **transfer** generation, .apprx.10% of the cells showed chromosome aberrations. Subculturing the neuroblasts for 4 **transfer** generations showed that malignancy (i.e., lethality to the host) as well as chromosomal abnormalities increased with time of subculture. Many virus-like particles were detected in l(2)gl4 neuroblasts after in vivo culture, whereas no such particles were detected in l(2)gl4 neuroblasts in situ in larvae. These particles contained RNAs homologous in sequence to the DNA of the movable element copia. They were indistinguishable from previously identified **retrovirus**-like particles in cultured Drosophila cells. Possibly the l(2)gl4 mutation reduces the genome integrity, resulting in transplantation-triggered genetic abnormalities, such as chromosomal abnormalities, increased transcription or replication of copia elements, and prodn. of **retrovirus**-like particles.

L4 ANSWER 92 OF 94 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:80638 CAPLUS
DOCUMENT NUMBER: 100:80638
TITLE: Characterization of human transforming genes from chemically transformed, teratocarcinoma, and pancreatic carcinoma cell lines
AUTHOR(S): Cooper, Colin S.; Blair, Donald G.; Oskarsson, Marianne K.; Tainsky, Michael A.; Eader, Lou A.; Woude, George F. Vande
CORPORATE SOURCE: Frederick Cancer Res. Facil., Natl. Cancer Inst., Frederick, MD, 21701, USA
SOURCE: Cancer Research (1984), 44(1), 1-10
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Dominant transforming genes that were **transferred** to mouse NIH3T3 cells by cellular DNAs prepd. from a chem. transformed human cell line (MNNG-HOS), a human teratocarcinoma cell line (PA1), and a human pancreatic carcinoma cell line (A1165) were characterized. The repetitive human DNA sequences that were assocd. with the transforming gene were examd., and their relationships to the oncogenes of the Harvey (rasH) and Kirsten (rasK) sarcoma viruses and to the human **neuroblastoma** transforming gene (rasN) were detd. Apparently, the transforming gene activated in the teratocarcinoma cell line is identical to the **neuroblastoma** transforming gene, and the transforming gene of the pancreatic carcinoma cell line is a human homolog of rasK. In contrast, the transforming gene activated in the chem. transformed human cell line showed no detectable homol. to rasK, rasH, and rasN.

L4 ANSWER 93 OF 94 MEDLINE
ACCESSION NUMBER: 83255007 MEDLINE
DOCUMENT NUMBER: 83255007 PubMed ID: 6347084
TITLE: Oncogene.
AUTHOR: Hagino-Yamagishi K; Toyoshima K
SOURCE: GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1983 Jul) 10 (7) 1557-63. Ref: 50
Journal code: 7810034. ISSN: 0385-0684.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198308
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 20020125
Entered Medline: 19830826
AB **Retroviruses** have long been fascinating to biologists because of

their capacity to induce neoplasms in various animals. The transformation of the cells by the viruses was due to their oncogene-products. The viral oncogenes were thought to be originated from DNA of normal cells by recombination events between **retroviruses** and cellular oncogenes. Recently, many cellular oncogenes were identified in human cancerous cells by the DNA **transfection** method, some of which were found to contain sequences related with already known viral oncogenes. On the other hand, the research on the relation between these oncogenes and chromosomal translocation associated with carcinogenesis is now in progress.

L4 ANSWER 94 OF 94 MEDLINE
ACCESSION NUMBER: 82272383 MEDLINE
DOCUMENT NUMBER: 82272383 PubMed ID: 6287287
TITLE: A transforming gene present in human sarcoma cell lines.
AUTHOR: Marshall C J; Hall A; Weiss R A
SOURCE: NATURE, (1982 Sep 9) 299 (5879) 171-3.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198210
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19821021

AB Morphological transformation of NIH/3T3 cells by **transfection** with DNA has been used to identify transforming sequences in human tumours. Transforming activity has been reported for DNAs isolated from bladder, mammary, colon and lung carcinomas, **neuroblastoma**, lymphoid and myeloid tumours. Each of these tissues seems to contain different transforming sequences except for the colon and lung tumours where the same sequence seems to be involved. We now report that in two different human sarcoma cell lines, a fibrosarcoma and an embryonal rhabdomyosarcoma, the DNAs have transforming activity. The transforming gene is the same in both sarcomas but differs from the activated sequences detected in other tumours. We have also found that the transforming gene has no detectable homology to eight **retrovirus** oncogenes tested.

murine **retroviruses** via the mH13 product.

L4 ANSWER 66 OF 94 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:286678 BIOSIS
DOCUMENT NUMBER: PREV199699009034
TITLE: Effective immunization against **neuroblastoma** using double-**transduced** tumor cells secreting GM-CSF and interferon-gamma.
AUTHOR(S): Bausero, Maria A.; Panoskaltsis-Mortari, Angela; Blazar, Bruce R.; Katsanis, Emmanuel (1)
CORPORATE SOURCE: (1) Univ. Minnesota, 420 Delaware St. S.E., Box 484, Minneapolis, MN 55455 USA
SOURCE: Journal of Immunotherapy with Emphasis on Tumor Immunology, (1996) Vol. 19, No. 2, pp. 113-124. ISSN: 1067-5582.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Murine **neuroblastoma**, neuro-2a, was **transduced** with the retroviral vector MFG-granulocyte-macrophage colony-stimulating factor (GM-CSF), to examine immune stimulation conferred by localized GM-CSF production. Expression of murine GM-CSF by neuro-2a (N-2a/GM) significantly reduced its tumorigenicity. Moreover, immunization of mice with irradiated N-2a/GM cells resulted in a significant protective effect against live tumor challenge 14 days later. Approximately 41% of mice immunized with irradiated N-2a/GM versus 0% of those vaccinated with irradiated parental tumor survived. Surviving mice were rechallenged after 50 days with wild-type neuro-2a or with the Sa1 syngeneic sarcoma to discern whether the generated immunity was durable and tumor specific. All mice survived wild-type neuro-2a challenge, whereas none survived inoculation with Sa1. Because both CD4+ and CD8+ T cells were necessary during priming to this MHC class I-lo, II- tumor, these data indicate that major histocompatibility complex (MHC) class I+, II+ antigen-presenting cells (APCs) were required for the T-cell antitumor response. Coexpression of GM-CSF and IFN-gamma, both of which have immunostimulatory activities on antigen-presenting cells, abrogated the tumorigenic potential of this tumor and increased immunogenicity over N-2a/IFN but not N-2a/GM. Vaccination of mice with preexisting retroperitoneal tumors with irradiated N-2a/GM and irradiated N-2a/IFN/GM improved survival. There was a trend for nonirradiated **transduced** cells to be more immunogenic than their irradiated counterparts. Immunohistochemistry of tissues from the vaccination site revealed a pronounced macrophage infiltration associated with nonirradiated N-2a/GM and N-2a/IFN/GM. These data suggest that vaccination involving nonirradiated **neuroblastoma** cells **transduced** with genes that stimulate APCs may be a useful approach in stimulating antitumor T-cell responses.

L4 ANSWER 67 OF 94 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:122242 CAPLUS
DOCUMENT NUMBER: 124:219668
TITLE: Gene therapy for **glioblastoma** in adult patients: Safety and efficacy evaluation of an in situ injection of recombinant **retroviruses** producing cells carrying the thymidine kinase gene of the herpes simplex type 1 virus, to be followed with the administration of ganciclovir
AUTHOR(S): Klatzmann, David; Philippon, Jacques; Valery, Charles A.; Bensimon, Gilbert; Salzmann, Jean-Loup
CORPORATE SOURCE: Hopital de la Pitie-Salpetriere, Universite Pierre et

Marie Curie, Paris, 75651/13, Fr.
SOURCE: Human Gene Therapy (1996), 7(1), 109-26
CODEN: HGTHE3; ISSN: 1043-03
PUBLISHER: Liebert
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This protocol aims at defining the safety and efficacy of an anticancer treatment for patients with a **glioblastoma** relapse. This treatment, sequentially administered to two different groups of patients in two escalating doses, consists in surgical injections within the surgical margin of the tumoral cavity of cells that produce recombinant **retroviruses**, followed with the administration of ganciclovir (GCV). This therapy is based on the introduction of a suicide gene within tumoral cells: the thymidine kinase gene from the herpes simplex type 1 (HSV1-TK) virus. This HSV1-TK gene sensitizes the cells to the toxicity of GCV, a drug without toxicity for normal cells, but one that kills those generating the HSV1-TK enzyme. Such destruction is restricted to dividing cells. Introducing the gene within tumoral cells is achieved through in situ injections of murine fibroblastic cells modified by genetic engineering (M11 cells). The latter constantly produce recombinant **retroviruses** contg. the HSV1-TK gene. Such **retroviruses** can only express their genes when the cells they have infected are in cycle. This is the reason why, once the M11 cells have been injected inside the tumor, the HSV1-TK gene is only expressed by tumoral cells and therefore, they, alone, are killed by GCV. Inversely, the normal cells of the surrounding brain tissue can neither be **transduced** nor sensitized to GCV toxicity in as much as they have no mitotic activity. Moreover, tumoral cells that do not express the gene, but are in the immediate vicinity of **transduced** ones, are also killed ("metabolic cooperation" effect, also restricted to dividing cells). Thus, it is not necessary for all tumoral cells to express the HSV1 gene in order for them to all be killed. The efficacy of the above therapeutic approach has been evidenced with animals in the treatment of brain tumors, of colic adenocarcinoma hepatic metastases and of malignant melanoma. A therapeutic trial on recurrent brain tumors or metastases has begun in the USA, using a similar approach. We propose a stage I-II clin. trial for the treatment of **glioblastoma** in adults. The patients to be included in this study have to show a relapsing **glioblastoma**. In spite of a renewed surgical intervention-the sole possible therapeutic action at this stage, most of the time-the median of survival for such patients does not exceed seven months. M11 cells are injected in situ in the wall of the tumoral cavity, after removal is judged macroscopically complete. The injected M11 cell-dose is adjusted to fit the size of the relapsing tumor, a size quantified by means of magnetic resonance (MRI) during the pre-selection period. Two dose-levels are planned with, at the second level, two extra injections on the 7th and 14th days, using an Ommaya reservoir. The injection of M11 cells is to be followed with a 10mg/kg/day i-v administration of GCV. For each dose-level, the safety and efficacy of the treatment are assessed using Fleming's sequential plan.

L4 ANSWER 68 OF 94 MEDLINE DUPLICATE 25
ACCESSION NUMBER: 96159035 MEDLINE
DOCUMENT NUMBER: 96159035 PubMed ID: 8567389
TITLE: Infectious **retrovirus** is inactivated by serum but not by cerebrospinal fluid or fluid from tumor bed in patients with malignant glioma.
AUTHOR: Shimizu K; Miyao Y; Tamura M; Kishima H; Ohkawa M; Mabuchi

E; Yamada M; Hayakawa T; Ikenaka K
CORPORATE SOURCE: Department of Neurosurgery, Osaka University Medical School.
SOURCE: JAPANESE JOURNAL OF CANCER RESEARCH, (1995 Nov) 86 (11) 1010-3.
Journal code: 8509412. ISSN: 0910-5050.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960315
Last Updated on STN: 19980206
Entered Medline: 19960304

AB Intravenous gene **transfer** using recombinant **retroviruses** tends to suffer from a low infectious viral titer when conducted in vivo. This is, in part, caused by complement-mediated proteolytic inactivation of the **retrovirus** in human serum. However, if the **retroviruses** were directly injected into the brain, they might not be inactivated. Supernatant from amphotropic **retrovirus** -producing cells harboring the BAG vectors was incubated with sera or cerebrospinal fluid (CSF) of patients with gliomas or unrelated disorders.

The **retroviruses** were severely inactivated in sera. However, no such inactivation was noted in CSF or fluid from the tumor bed of glioma patients. These data suggest that gene **transfer** using recombinant **retroviruses** could be done into the cavity after removal of the tumor in glioma patients.

L4 ANSWER 69 OF 94 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:373293 CAPLUS
DOCUMENT NUMBER: 122:157495
TITLE: Single cell monitoring of growth arrest and morphological changes induced by **transfer** of wild-type p53 alleles to **glioblastoma** cells
AUTHOR(S): Van Meir, Erwin G.; Roemer, Klaus; Diserens, Annie-Claire; Kikuchi, Tetsuro; Rempel, Sandra A.; Haas, Martin; Huang, H.-J. Su; Friedmann, Theodore; de Tribolot, Nicolas; Cavenee, Webster K.
CORPORATE SOURCE: Ludwig Inst. for Cancer Research, Univ. of California, San Diego, La Jolla, CA, 92093, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1995), 92(4), 1008-12
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mutation of the p53 tumor suppressor gene is one of the earliest identified genetic lesions during malignant progression of human astrocytomas. To assess the functional significance of these mutations, wild-type (WT) p53 genes were introduced into **glioblastoma** cell lines having mutant, WT, or null endogenous p53 alleles. Populations of cells with mutant or null endogenous p53 alleles and exogenous WT p53 were spontaneously selected in culture for cells expressing only mutant p53 or no p53, which then displayed a growth and tumorigenic phenotype identical to the parental cells. To det. the phenotypic consequences of WT p53 expression before the occurrence of mutations, we developed a single cell assay to monitor WT p53-dependent transcription activity.

Transfer and expression of exogenous WT p53 genes to cells with endogenous mutant or deleted, but not WT, p53 alleles caused growth arrest and morphol. changes, including increased cell size and acquisition of

multiple nuclei. This supports the hypothesis that genetic lesions of the p53 gene play a[redacted]mportant role in the genesis o[redacted]strocytomas. Furthermore, the high sensitivity of the episomal single cell reporter strategy developed here has potential clin. applications in the rapid screening of patients for germ-line mutations of the p53 gene or any other gene with known targets for transcriptional transactivation.

L4 ANSWER 70 OF 94 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:970347 CAPLUS
DOCUMENT NUMBER: 124:53321
TITLE: Characteristics and immunomodulatory properties of human **neuroblastoma** cells after **retrovirus**-mediated gene **transfer** of the cytokine genes IL-2 and IFN-.gamma.
AUTHOR(S): Coze, C.; Aalto-Setala, K.; Brenner, M.; Chiang, Y.; Gangavalli, R.; Leimig, T.
CORPORATE SOURCE: Department of Hematology/Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA
SOURCE: Transgenics (1995), 1(6), 585-95
CODEN: TADTEF; ISSN: 1023-6171
PUBLISHER: Harwood
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have studied the feasibility and consequences of **transferring** the cytokine genes IL-2 and IFN-.gamma. into human **neuroblastoma** cells to generate cytokine-secreting tumor cell lines for use as in vivo immunogens. Retroviral vectors were used to **transduce** six **neuroblastoma** cell lines with NeoR alone or NeoR with IL-2 or IFN-.gamma.. None of the parental or Neo **transduced** lines secreted either cytokine; the cytokine-**transduced** lines secreted high levels of the corresponding cytokine after NeoR selection. All NeoR as well as IL-2 lines were morphol. identical to the parental control. However, in three of the five lines successfully **transduced** with the IFN-.gamma. gene, expression of this cytokine slowed cell growth and induced terminal differentiation. The immunomodulatory effects of each cytokine were different. Cell surface levels of the adhesion mols. ICAM I (CD 54) and LFA3 (CD58) were unaffected by the expression of either cytokine gene, but HLA class I and II mols. on previously neg. cell lines were upregulated by IFN-.gamma.. Co-culture of mononuclear cells with cytokine **transduced** cell lines showed that IL-2 but not IFN-.gamma. **transduced** tumor cells increased the proportion of activated (CD3+DR+) and memory cells (CD3+CD45RO+) in the lymphocyte population. Both IL-2 and IFN-.gamma. **transduced** tumor cells were able to increase cytotoxicity and proliferation against parental tumor lines, but the effect was more striking and more consistent with IL-2. Thus, IFN-.gamma. and IL-2 **transduction** of human **neuroblastoma** cells produces distinguishable but potentially complementary effects on immunomodulation of the tumor or of the host immune system. These data form part of the pre-clin. justification supporting current and future tumor vaccine studies using **neuroblastoma** cells **transduced** with each cytokine individually and in combination.

L4 ANSWER 71 OF 94 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:186690 BIOSIS
DOCUMENT NUMBER: PREV199598200990
TITLE: Characterization of a human **glioblastoma** cell line **transduced** with the cDNA encoding tumor necrosis factor (huTNF-a.
AUTHOR(S): Ioli, G. (1); Tocco, L.; Graff, M.; Cruzen, M.; Santin, A.;

Granger, G.; Jacques, D.; Hiserodt, J.
CORPORATE SOURCE: (1) Dep. Molecular Biol. Biochem. Pathology, Univ. California Irvine, Irvine, CA USA
SOURCE: Proceedings of the American Association for Cancer Research
Annual Meeting, (1995) Vol. 36, No. 0, pp. 420.
Meeting Info.: Eighty-sixth Annual Meeting of the American Association for Cancer Research Toronto, Ontario, Canada March 18-22, 1995
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 72 OF 94 MEDLINE
ACCESSION NUMBER: 95227867 MEDLINE
DOCUMENT NUMBER: 95227867 PubMed ID: 7712334
TITLE: Long-term rat survival after malignant brain tumor regression by retroviral gene therapy.
AUTHOR: Izquierdo M; Cortes M; de Felipe P; Martin V; Diez-Guerra J; Talavera A; Perez-Higueras A
CORPORATE SOURCE: Departamento de Biologia Molecular, Universidad Autonoma de
Madrid, Facultad de Ciencias, Spain.
SOURCE: GENE THERAPY, (1995 Jan) 2 (1) 66-9.
Journal code: 9421525. ISSN: 0969-7128.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950524
Last Updated on STN: 19970203
Entered Medline: 19950512
AB Total regression of malignant brain tumors was observed in Wistar rats after **retrovirus**-mediated gene therapy. Tumors were induced by inoculation of C6 rat **glioblastoma** cells to a specific location in the rat brain and the tumors that developed were visualized by magnetic resonance imaging (MR). Retroviral vectors were constructed from a defective murine **retrovirus** to which the thymidine kinase (tk 1) gene from herpes simplex was added (HSV1tk). The vectors produced therapeutic viruses upon their introduction into **retrovirus** packaging cells. Delivery of the producer cells to the tumor mass and subsequent antiherpetic treatment eradicated the tumors completely, as observed using MRI. Some of the treated animals have been followed for over 8 months and show no signs of recurrence.

L4 ANSWER 73 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 26
ACCESSION NUMBER: 1995:439008 CAPLUS
DOCUMENT NUMBER: 122:211573
TITLE: Human class II major histocompatibility complex gene **transfer** into murine **neuroblastoma** leads to loss of tumorigenicity, immunity against subsequent tumor challenge, and elimination of microscopic pre-established tumors
AUTHOR(S): Hock, Randy A.; Reynolds, Brian D.; Tucker-McClung, Cheryl L.; Kwok, William W.
CORPORATE SOURCE: Herman B. Wells Center for Pediatric Research, Riley Hospital for Children, Indianapolis, IN, USA
SOURCE: Journal of Immunotherapy with Emphasis on Tumor Immunology (1995), 17(1), 12-18
CODEN: JIEIEZ; ISSN: 1067-5582
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Immunol. recognition of transformed cells is critically important to limit

tumor development and proliferation. Because established tumors have escaped immune recognition and elimination, novel strategies to enhance antitumor immun[redacted] have been developed. A uniqu[redacted]pproach has used the introduction of genes encoding major histocompatibility complex (MHC) antigens into tumor cells. Expts. in mice have shown that the expression of syngeneic class II MHC antigens in tumor cells completely abrogates tumorigenicity and induces tumor-specific immunity. In this study the authors sought to det. whether a more effective antitumor immune response would be generated by introducing xenogeneic class II MHC genes into tumor cells. To address this question the authors used recombinant **retroviruses** to express human class II MHC genes in a highly malignant murine **neuroblastoma** cell line, Neuro-2a. The authors found that normal mice inoculated with Neuro-2a expressing the human class II MHC antigen did not develop tumors and were immune to subsequent challenge with unmodified Neuro-2a cells. In addn., mice bearing small established Neuro-2a tumors were cured by vaccination with Neuro-2a expressing human class II MHC. The authors hypothesize that a similar approach using retroviral-mediated **transduction** of class II MHC genes into human tumor cells may be an effective alternative to current cancer treatment.

L4 ANSWER 74 OF 94 MEDLINE DUPLICATE 27
ACCESSION NUMBER: 95191764 MEDLINE
DOCUMENT NUMBER: 95191764 PubMed ID: 7885554
TITLE: Bystander tumoricidal effect in the treatment of experimental brain tumors.
AUTHOR: Wu J K; Cano W G; Meylaerts S A; Qi P; Vrionis F; Cherington V
CORPORATE SOURCE: Department of Neurosurgery, Tufts University School of Medicine, Boston, Massachusetts.
CONTRACT NUMBER: CA44761 (NCI)
P30DK34928 (NIDDK)
SOURCE: NEUROSURGERY, (1994 Dec) 35 (6) 1094-102; discussion 1102-3.
Journal code: 7802914. ISSN: 0148-396X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950425
Last Updated on STN: 19970203
Entered Medline: 19950413

AB The **retrovirus**-mediated **transfer** of the herpes simplex virus-thymidine kinase (HSV-tk) gene into tumor cells renders them sensitive to the cytocidal effect of the antiviral drug ganciclovir. This method has shown promising results as a treatment for experimental brain tumors. These experiments indicate that a major mechanism for the effectiveness of HSV-tk retroviral gene therapy may be the bystander tumoricidal effect. The bystander effect was hypothesized to explain tumor eradication, given that the efficacy of in vivo gene **transfer** to tumor cells was less than 100%. We demonstrate, in this report, that the bystander tumoricidal effect is a major contributor to the tumoricidal effect of ganciclovir in cell culture experiments using the mouse K1735 C19 cerebral melanoma line, thereby expanding the observation of the bystander phenomenon to a broader range of tumor types. The bystander effect was studied in vitro by coculturing wild-type C19 melanoma cells with HSV-tk-expressing C19 (C19-STK) cells. A maximal tumoricidal effect was seen when only 1 in 10 tumor cells expressed the HSV-tk gene. This suggests that in effect, 1 tumor cell with the HSV-tk gene, when given ganciclovir, will destroy 10 neighboring or bystander cells. The destruction of bystander cells does not appear to be mediated by a soluble

factor(s) released into the media but, rather, requires close cell proximity or cell contact. In addition, HSV-tk-expressing C19 cells can exert an antitumoral effect not only on wild-type C19 cells but also on cells from a variety of different tumor cell lines, including a human **glioblastoma** multiforme cell line, indicating that the bystander effect is not a cell line-specific phenomenon. Finally, we observed that the bystander tumoricidal effect could be harnessed directly without using **retrovirus**-producing cells to increase survival in the mouse C19 brain tumor model. The potential implications of our findings in treating human brain tumors are discussed.

L4 ANSWER 75 OF 94 MEDLINE
ACCESSION NUMBER: 94150653 MEDLINE
DOCUMENT NUMBER: 94150653 PubMed ID: 8107827
TITLE: **Glioblastoma** growth inhibited in vivo by a dominant-negative Flk-1 mutant.
AUTHOR: Millauer B; Shawver L K; Plate K H; Risau W; Ullrich A
CORPORATE SOURCE: Department of Molecular Biology, Max-Planck-Institut fur Biochemie, Martinsried, Germany.
SOURCE: NATURE, (1994 Feb 10) 367 (6463) 576-9.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940330
Last Updated on STN: 20000303
Entered Medline: 19940324

AB Angiogenesis, the sprouting of capillaries from pre-existing blood vessels, is a fundamental process in the formation of the vascular system during embryonic development. In adulthood, angiogenesis takes place during corpus luteum formation and in pathological conditions such as wound healing, diabetic retinopathy, and tumor-igenesis. Vascularization is essential for solid tumour growth and is thought to be regulated by tumour cell-produced factors, which have a chemotactic and mitogenic effect on endothelial cells. Vascular endothelial growth factor (VEGF), a homodimeric glycoprotein of relative molecular mass 45,000, is the only mitogen, however, that specifically acts on endothelial cells, and it may be a major regulator of tumour angiogenesis in vivo. Its expression has been shown to be upregulated by hypoxia, and its cell-surface receptor, Flk-1, is exclusively expressed in endothelial cells. Here we investigate the biological relevance of the VEGF/Flk-1 receptor/ligand system for angiogenesis using a **retrovirus** encoding a dominant-negative mutant of the Flk-1/VEGF receptor to infect endothelial target cells in vivo, and find that tumour growth is prevented in nude mice. Our results emphasize the central role of the Flk-1/VEGF system in angiogenesis in general and in the development of solid tumours in particular.

L4 ANSWER 76 OF 94 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:260589 CAPLUS
DOCUMENT NUMBER: 122:29623
TITLE: Immunomodulatory effects of human **neuroblastoma** cells **transduced** with a retroviral vector encoding interleukin-2
AUTHOR(S): Leimig, Thasia; Foreman, Nicholas; Rill, Donna; Coze, Carole; Holladay, Martha; Brenner, Malcolm
CORPORATE SOURCE: Department of Hematology/Oncology, St Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Cancer Gene Therapy (1994), 1(4), 253-8
CODEN: CGTHEG; ISSN: 0929-1903
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have investigated whether retroviral mediated **transfer** of the IL-2 gene renders human **neuroblastoma** cells immunogenic,

justifying their use in a clin. tumor immunization study. Fourteen **neuroblastoma** cell lines were established from patients with disseminated **neuroblastoma** and **transduced** with the vector G1Ncv12, which contains the neomycin phosphotransferase gene and the cDNA of the human interleukin-2 gene. Clones secreting >150 pg/106 cells/24 h of IL-2 were selected for further study. Secretion of IL-2 was maintained for at least 3 wk in nonselective media, implying that prodn. of the cytokine would continue under in vivo conditions. Co-culture of IL-2 **transduced** cell lines with patient lymphocytes induced potent cytotoxic activity against both **transduced** and parental **neuroblastoma** cell lines. This activity was HLA unrestricted, and predominantly mediated by CD16+ or CD56+ and CD8- lymphocytes. These data form the preclin. justification for our current immunization protocol for patients with relapsed or resistant **neuroblastoma**.

L4 ANSWER 77 OF 94 MEDLINE
ACCESSION NUMBER: 94295991 MEDLINE
DOCUMENT NUMBER: 94295991 PubMed ID: 8024195
TITLE: Gene marking and autologous bone marrow transplantation.
AUTHOR: Brenner M K; Rill D R; Moen R C; Krance R A; Heslop H E; Mirro J Jr; Anderson W F; Ihle J N
CORPORATE SOURCE: Department of Hematology/Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105.
CONTRACT NUMBER: CA 21765 (NCI)
CA 58211 (NCI)
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1994 May 31) 716 204-14; discussion 214-5, 225-7. Ref: 37
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940815
Last Updated on STN: 19940815
Entered Medline: 19940804

AB If residual cancer cells in harvested bone marrow could be marked and subsequently detected in patients at relapse, valuable information would be obtained about the source of recurrent disease after autologous marrow transplantation. If normal progenitor cells were also marked, the study would provide useful data on the susceptibility of these human cells to gene **transfer** and their capacity to express newly introduced genes. We **transferred** the neomycin-resistance gene (NeoR) into bone marrow cells harvested from 20 children with acute myeloid leukemia (n = 12) or **neuroblastoma** (n = 8) in clinical and cytological remission using a **retrovirus** vector. The cells were then returned to the patients as part of an autologous bone marrow transplantation protocol. Two AML and three **neuroblastoma** patients have relapsed. In all, the resurgent cells contained the NeoR marker by analysis with PCR. These results prove that so-called remission marrow can contribute to relapse in patients who receive autologous transplants. The gene marking technique is now being used to evaluate techniques of pretransplant purging.

L4 ANSWER 78 OF 94 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:45928 CAPLUS
DOCUMENT NUMBER: 120:45928
TITLE: Methods and compositions for gene, tumor, and viral infection therapy and prevention of programmed cell death (apoptosis)
INVENTOR(S): Roizman, Bernard; Chou, Joany
PATENT ASSIGNEE(S): Arch Development Corp., USA

SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9319591	A1	19931014	WO 1993-US1801	19930226
W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9337818	A1	19931108	AU 1993-37818	19930226
AU 682463	B2	19971009		
JP 07507997	T2	19950907	JP 1993-517439	19930226
EP 675961	A1	19951011	EP 1993-907093	19930226
EP 675961	B1	20021127		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 6172047	B1	20010109	US 1995-483533	19950607
US 6340673	B1	20020122	US 1999-283471	19990401

PRIORITY APPLN. INFO.:
US 1992-861233 A 19920331
WO 1993-US1801 A 19930226
US 1995-419853 B3 19950411
US 1995-483533 A1 19950607

AB Programmed cell death in neurons is prevented or treated by gene therapy using a nonpathogenic vector contg. the .gamma.134.5 gene of herpes simplex virus type 1 (HSV-1), or by treatment with the expression product of this gene, protein ICP34.5, or its functional equivs. The function of .gamma.134.5 is to protect infected nerve cells from shutoff of protein synthesis and consequent programmed cell death, thereby promoting neuronal survival and virus replication and spreading; .gamma.134.5 and ICP34.5 may thus extend the lifetime of nonregenerating neurons in neurodegenerative diseases. The .gamma.134.5 gene and its product also protect neurons and other cells from environmental stresses which may lead to apoptosis, e.g. UV and NGF deprivation. Candidate drugs for extending the viability of cells are screened in **neuroblastoma** cells contg. or lacking the .gamma.134.5 gene by applying such stresses and subsequently measuring the cells' viability. The vector may be HSV-1 or HSV-2 altered by deletion of the ICP4, .alpha.4, or .alpha.0 gene to render it nonpathogenic, an altered **retrovirus**, vaccinia virus, picornavirus, coronavirus, bunyavirus, togavirus, or rhabdovirus, or a multipotent neural cell line. Thus, a mouse cerebellar progenitor cell line was **transduced** with replication-incompetent retroviral vector BAG contg. gene .gamma.134.5, then cocultured with a primary culture of dissocd. neonatal mouse cerebellum cells which were finally injected into newborn mice to prevent neuronal degeneration.

L4 ANSWER 79 OF 94 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:64568 BIOSIS
DOCUMENT NUMBER: PREV199497077568
TITLE: Gene therapy of cancer.
AUTHOR(S): Freeman, Scott M. (1); Zwiebel, James A.
CORPORATE SOURCE: (1) Dep. Lab. Med. Pathol., Div. Transfusion Med., Tulane Univ., New Orleans, LA USA
SOURCE: Cancer Investigation, (1993) Vol. 11, No. 6, pp. 676-688. ISSN: 0735-7907.
DOCUMENT TYPE: General Review
LANGUAGE: English

AB Retroviral-mediated gene **transfer** has permitted the development of clinical protocols for the study and treatment of cancer. These protocols can be divided into gene-labeling and gene therapy proposals. Labeling studies include the tracking of tumor infiltrating lymphocytes (TIL) following the administration of those cells, and the detection, at the time of relapse, of tumor cells from transplanted autologous bone marrow. Most gene therapy protocols are designed to induce an immune attack against the tumor by inserting genes into tumor cells themselves. Although uncertainty about the safety of the procedure still exists, gene therapy of cancer holds much promise as an effective treatment modality.

L4 ANSWER 80 OF 94 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:379338 BIOSIS
DOCUMENT NUMBER: PREV199345050763
TITLE: In vivo assessment of therapy on human carcinomas **transduced** with STK gene.
AUTHOR(S): Chu, M. Y. W. (1); Lipsky, M. H.; Whartenby, K. A.; Freeman, S.; Chen, T. M.; Epstein, J.; Forman, E. N.; Calabresi, P.
CORPORATE SOURCE: (1) Dep. Med., Rhode Island Hosp., Brown Univ., Providence, RI 02903
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1993) Vol. 34, No. 0, pp. 337.
Meeting Info.: 84th Annual Meeting of the American Association for Cancer Research Orlando, Florida, USA May 19-22, 1993
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 81 OF 94 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:10466 BIOSIS
DOCUMENT NUMBER: PREV199497023466
TITLE: **Retrovirus** mediated **transfer** of human p68 kinase gene into human **neuroblastoma** cells.
AUTHOR(S): Higuchi, Takakazu (1); Williams, Bryan R. G.
CORPORATE SOURCE: (1) Dep. Cancer Biol., Res. Inst., The Cleve. Clin. Found., Cleveland, OH 44195 USA
SOURCE: Journal of Interferon Research, (1993) Vol. 13, No. SUPPL. 1, pp. S122.
Meeting Info.: Annual Meeting of the ISICR (International Society for Interferon and Cytokine Research) on the Interferon System Tokyo, Japan October 24-28, 1993
ISSN: 0197-8357.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 82 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 28
ACCESSION NUMBER: 1992:401942 CAPLUS
DOCUMENT NUMBER: 117:1942
TITLE: Comparison of rabies virus G proteins produced by cDNA-**transfected** animal cells that display either inducible or constitutive expression of the gene
AUTHOR(S): Morimoto, Kinjiro; Kawai, Akihiko; Mifune, Kumato
CORPORATE SOURCE: Fac. Pharm. Sci., Kyoto Univ., Kyoto, 606, Japan
SOURCE: Journal of General Virology (1992), 73(2), 335-45
CODEN: JGVIAY; ISSN: 0022-1317
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A **retrovirus** expression vector, pZIP-NeoSV(X)1, was used to introduce a cloned cDNA of the rabies virus G gene into BHK-21 cells and the NA cell clone originated from the murine **neuroblastoma** C1300

line. The neomycin resistance gene of the vector was used to isolate several G418-resistant transformants of BHK-21 and NA cells (referred to as G-BHK and G-NA cells, resp.). G-BHK cells constitutively produced G proteins, whereas G-NA cells produced the proteins only when treated with sodium butyrate. G proteins synthesized in these transformants were transported normally to the surface of the cell, but they displayed different electrophoretic mobilities, which were shown to originate from differences in the no. and structure of the carbohydrate moieties of the protein. G-BHK cells produced highly glycosylated and sialylated G proteins, whereas G proteins with less glycosylation and much less sialylation were produced by G-NA cells as obsd. in virus-infected NA and BHK-21 cells, indicating that the glycosylation and sialylation of the G protein depend on the cellular conditions under which the protein was produced. In the absence of sodium butyrate, the G protein was not detectable in G-NA cells either by immunoblot assay or fluorescent antibody staining, but the cells were fairly sensitive to syngeneic rabies virus-specific cytotoxic T lymphocytes, although the sensitivity was much increased by treatment with sodium butyrate.

L4 ANSWER 83 OF 94 MEDLINE
ACCESSION NUMBER: 93003506 MEDLINE
DOCUMENT NUMBER: 93003506 PubMed ID: 1391032
TITLE: **Retrovirus**-mediated gene **transfer** as an approach to analyze **neuroblastoma** relapse after autologous bone marrow transplantation.
AUTHOR: Rill D R; Buschle M; Foreman N K; Bartholomew C; Moen R C; Santana V M; Ihle J N; Brenner M K
CORPORATE SOURCE: Department of Hematology/Oncology, St. Jude Children's Research Hospital, Memphis, TN 38101.
CONTRACT NUMBER: CA 21765 (NCI) CA23099 (NCI)
SOURCE: HUMAN GENE THERAPY, (1992 Apr) 3 (2) 129-36. Journal code: 9008950. ISSN: 1043-0342.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199210
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921026

AB Disseminated **neuroblastoma** is a malignancy of children often treated by intensive chemotherapy/radiotherapy followed by autologous bone marrow transplantation (ABMT). A high proportion of those treated subsequently relapse. It is unknown if relapse is a consequence of residual disease in the patient or of contaminating malignant cells remaining in the infused marrow, which, of necessity, is harvested and stored prior to ablative chemotherapy/radiotherapy. The assumption that residual cells in the infused marrow contribute to relapse has lead to the adoption of marrow purging prior to reinfusion. However, neither the necessity nor the efficacy of the procedure have been established. We now show how retroviral-mediated gene **transfer** using the LNL6 vector may resolve this issue. Clonogenic **neuroblastoma** cells in patient marrow can be **transduced** and the NEOR gene detected by observing individual **neuroblastoma** cell colony growth in G418, and by polymerase chain reaction (PCR) of individual colonies. Efficiency of **transduction** is between 0 and 13.5%. If marrow is exposed to LNL6 prior to infusion and marked cells are detected at the time of relapse, this would demonstrate that infused marrow contributed to disease recurrence. The technique could then be used to analyze the efficacy of marrow purging techniques. Since normal progenitor cells from these patients are also marked, the technique can be used to study factors that

in glioma or fibroblast cells. Deletion studies revealed that the proximal 193-base pair region, which contains the downstream transcription initiation site but not the upstream site, is essential for the Math3 promoter activity and can direct efficient expression in **neuroblastoma** cells. In contrast, **retrovirus**-mediated promoter anal. demonstrated that a region further upstream is addnl. necessary for retinal expression. These results indicate that Math3 promoter contains two essential regulatory regions, the proximal 193-base pair region, which confers efficient neural-specific expression, and a region further up-stream, required for retinal expression.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 49 OF 94 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:10247 CAPLUS

DOCUMENT NUMBER: 130:151527

TITLE: A constitutively active epidermal growth factor receptor cooperates with disruption of G1 cell-cycle arrest pathways to induce glioma-like lesions in mice

AUTHOR(S): Holland, Eric C.; Hively, Wendy P.; DePinho, Ronald A.; Varmus, Harold E.

CORPORATE SOURCE: Div. Basic Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA

SOURCE: Genes & Development (1998), 12(23), 3675-3685
CODEN: GEDEEP; ISSN: 0890-9369

PUBLISHER: Cold Spring Harbor Laboratory Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The epidermal growth factor receptor (EGFR) gene is amplified or mutated in 30%-50% of human **glioblastoma** multiforme (GBM). These mutations are assocd. usually with deletions of the INK4a-ARF locus, which encodes two gene products (p16INK4a and p19ARF) involved in cell-cycle arrest and apoptosis. We have investigated the role of EGFR mutation in gliomagenesis, using avian retroviral vectors to **transfer** a mutant EGFR gene to glial precursors and astrocytes in transgenic mice expressing tv-a, a gene encoding the **retrovirus** receptor TVA, under control of brain cell type-specific promoters. We demonstrate that expression of a constitutively active, mutant form of EGFR in cells in the glial lineage can induce lesions with many similarities to human gliomas. These lesions occur more frequently with gene **transfer** to mice expressing tv-a from the progenitor-specific nestin promoter than to mice expressing tv-a from the astrocyte-specific glial fibrillary acidic protein (GFAP) promoter, suggesting that tumors arise more efficiently from immature cells in the glial lineage. Furthermore, EGFR-induced gliomagenesis appears to require addnl. mutations in genes encoding proteins involved in cell-cycle arrest pathways. We have produced these combinations by simultaneously infecting tv-a transgenic mice with vectors carrying cdk4 and EGFR or by infecting tv-a transgenic mice bearing a disrupted INK4a-ARF locus with the EGFR-carrying vector alone. Moreover, EGFR-induced gliomagenesis does not occur in conjunction with p53 deficiency, unless the mice are also infected with a vector carrying cdk4. The gliomagenic combinations of genetic lesions required in mice are similar to those found in human gliomas.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 50 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 18
ACCESSION NUMBER: 1998:778563 CAPLUS
DOCUMENT NUMBER: 130:133798
TITLE: A phase I/II study of herpes simplex virus type 1 thymidine kinase "suicide" gene therapy for recurrent **glioblastoma**
AUTHOR(S): Klatzmann, David; Valery, Charles A.; Bensimon, Gilbert; Marro, Beatrice; Boyer, Olivier; Mokhtari, Karima; Diquet, Bertrand; Salzmann, Jean-Loup; Philippon, Jacques
CORPORATE SOURCE: The Study Group on Gene Therapy for Glioblastoma, Department of Immunology, Hopital Pitie-Salpetriere, Paris, 75651, Fr.
SOURCE: Human Gene Therapy (1998), 9(17), 2595-2604
CODEN: HGTHE3; ISSN: 1043-0342
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Despite extensive surgery for **glioblastoma**, residual tumor cells always lead to relapse. Gene therapy based on **retrovirus** -mediated gene **transfer** of herpes simplex virus type 1 thymidine kinase (HSV-1 TK), which specifically sensitizes dividing cells to ganciclovir (GCV) toxicity, may help eradicate such cells. During **glioblastoma** surgery, HSV-1 TK retroviral vector-producing cells (M11) were injected into the surgical cavity margins after tumor debulking. After a 7-day **transduction** period, GCV was administered for 14 days. Safety was assessed by clin. and lab. evaluations, and efficacy was assessed by MRI-based relapse-free survival at month 4 and by overall survival. Twelve patients with recurrent **glioblastoma** were treated without serious adverse events related to M11 cell administration or GCV. Quality of life was not neg. influenced by this treatment. Overall median survival was 206 days, with 25% of the patients surviving longer than 12 mo. At 4 mo after treatment, 4 of 12 patients had no recurrence; their median overall survival was 528 days, compared with 194 days for patients with recurrence ($p = 0.03$ by the log rank test). One patient is still free of detectable recurrence, steroid free and independent, 2.8 yr after treatment. Thus, brain injections of M11 retroviral vector-producing cells for **glioblastoma** HSV-1 TK gene therapy were well tolerated and assocd. with significant therapeutic responses. These results warrant further development of this therapeutic strategy in brain tumor, including recurrent **glioblastoma**.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 51 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 19
ACCESSION NUMBER: 1998:607516 CAPLUS
DOCUMENT NUMBER: 129:339526
TITLE: In vitro and in vivo effects of **retrovirus** -mediated **transfer** of the connexin 43 gene in malignant gliomas: consequences for HSVtk/GCV anticancer gene therapy
AUTHOR(S): Cirenei, N.; Colombo, B. M.; Mesnil, M.; Benedetti, S.; Yamasaki, H.; Finocchiaro, G.
CORPORATE SOURCE: Istituto Nazionale Neurologico C Besta, Divisione di Biochimica e Genetica, Unita di Neuro-Oncologia Molecolare e Terapia Genica, Milan, 20133, Italy
SOURCE: Gene Therapy (1998), 5(9), 1221-1226
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In tumors, gap junctional intercellular communication (GJIC) is usually down-regulated and the expression of connexins, membrane proteins constituting gap junction channels, is often low or altered. GJIC, allowing the intercellular diffusion of ganciclovir (GCV) triphosphate, is also one mediator of the "bystander effect", the phenomenon by which herpes simplex virus thymidine kinase (HSVtk)-**transduced**, neoplastic cells kill surrounding HSVtk-neg. cells when treated with GCV. The authors set up expts. to evaluate the effects of **retrovirus** -mediated in vivo gene **transfer** of connexin 43 in malignancies with low GJIC capacity. The authors found that U-87 human **glioblastoma** cells **transfected** in vitro by the human Cx43 cDNA grow more slowly than control U-87 cells and lose their tumorigenicity when injected s.c. in nude mice. When the Cx43 gene was **transduced** in vitro in U-87 cells by a retroviral producer cell line (N3.2.ii, titer 1.5 .times. 106 c.f.u./mL) in vivo results were similar. However, only when U-87 cells were co-injected with N3.2.ii cells in nude mice in a 1:5 ratio, a 50% redn. in tumor size was obtained during the first 3 wk. Moreover the coinjection of U-87 cells with N3.2.ii and SBA cells (a retroviral producer cell line expressing the HSVtk gene), was not able to potentiate the effects of GCV administration, suggesting that Cx43 gene **transfer** requires more efficient vectors to increase the bystander effect in vivo.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 52 OF 94 MEDLINE

ACCESSION NUMBER: 1999081926 MEDLINE
DOCUMENT NUMBER: 99081926 PubMed ID: 9863029
TITLE: Use of gene marking technologies in oncology.
AUTHOR: Brenner M
CORPORATE SOURCE: Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, Texas 77030, USA.
SOURCE: FORUM, (1998 Oct-Dec) 8 (4) 342-53. Ref: 67
Journal code: 9315183. ISSN: 1121-8142.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990216
Last Updated on STN: 19990216
Entered Medline: 19990129

AB Investigation of the mechanism of relapse in patients receiving stem cell rescue as therapy for malignant disease has been facilitated by gene marking studies. These studies have shown the marker gene to be present in malignant cells in the patient at the time of relapse, indicating that infused stem cells can contribute to disease recurrence. As normal progenitor cells are also marked and can be tracked in vivo, these studies have also helped us learn how haemopoietic stem cells respond to manipulation, for example with growth factors. Second generation studies with multiple, modified vectors are beginning to provide information about a wider variety of clinical and biological issues, including the efficacy of purging. Although marker studies have been useful for haematological malignancy and for **neuroblastoma**, they are hampered by the low efficiency of marking achieved by retroviral vectors. For many malignancies, marking efficiencies are insufficient for useful information

to be obtained. This problem may be overcome by the introduction of vectors that, unlike **retroviruses**, can stably integrate in cells that are not in [redacted]cle at the time of vector expos[redacted]e. Other improvements will focus on the marker genes themselves, using marker elements that are simpler to track and will not produce any modification of the cells' behaviour. Finally, marker studies have proved safe so far, but follow-up of the treated patients continues.

L4 ANSWER 53 OF 94 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:97853 BIOSIS
DOCUMENT NUMBER: PREV199900097853
TITLE: Gene **transfer**: A review of methods and applications.
AUTHOR(S): Prince, H. Miles (1)
CORPORATE SOURCE: (1) Division Hematology Medical Oncology, Peter MacCallum Cancer Institute, Locked Bag 1, A Beckett St., Melbourne, Vic. 3000 Australia
SOURCE: Pathology, (Nov., 1998) Vol. 30, No. 4, pp. 335-347. ISSN: 0031-3025.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB Gene **transfer** is a potentially powerful tool for the treatment of a wide variety of diseases. The **transfer** of these genes is achieved by utilizing a variety of vectors, including retroviral, adenoviral, adeno-associated virus (AAV) and a number of non-viral mechanisms. Numerous studies have successfully demonstrated **transduction** of genes into target cells with a variety of vectors, and have provided 'proof-in-principle' that gene **transfer** can result in prolonged in vivo expression of **transduced** genes, albeit at low quantities. Furthermore, gene marking studies in acute myeloblastic leukemia (AML), chronic myeloid leukemia (CML) and **neuroblastoma** have elegantly demonstrated that gene-marked tumor cells contribute to relapse following autologous transplantation. However none of the studies examining the therapeutic benefit of gene therapy has definitively demonstrated a clinically meaningful benefit. Nonetheless, the results of studies involving gene **transfer** for severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), melanoma and lung cancer highlight the potential benefit of this strategy.
This review will discuss mechanisms of achieving gene **transfer** into target cells. It will examine some of the pre-clinical and clinical results to date and will discuss some of the potential uses of gene **transfer** for therapeutic purposes.

L4 ANSWER 54 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 20
ACCESSION NUMBER: 1998:403765 CAPLUS
DOCUMENT NUMBER: 129:180024
TITLE: Cancer gene therapy using suicide genes
AUTHOR(S): Berenstein, Mariana; Adris, Soraya; Ledda, Fernanda; Wolfmann, Claudia; Medina, Jorge; Bravo, Alicia; Mordoh, Jose; Chernajovsky, Yuti; Podhajcer, Osvaldo L.
CORPORATE SOURCE: Fundacion Campomar, Univ. Buenos Aires, Argent.
SOURCE: Medicina (Buenos Aires) (1998), 58(2), 185-188 CODEN: MEDCAD; ISSN: 0025-7680
PUBLISHER: Sociedad Argentina de Investigacion Clinica
DOCUMENT TYPE: Journal
LANGUAGE: Spanish
AB Tumor cells **transfected** with **retrovirus** carrying the herpes simplex-1 virus thymidine kinase (HSV-tk) are capable of transforming the antiviral drug ganciclovir (GCV) into a metabolic form only toxic to dividing cells. The efficacy of this suicide gene therapy is increased by a "bystander" effect resulting not only in the death of the recipient cell, but also in the death of non modified surrounding cells. Even though the mechanism of this "bystander" effect remains to be

elucidated, strong evidence suggest that the immune system plays a main role to achieve complete tumor eradication. In the present study we evaluate the efficiency of this suicide system on three different tumor models: one human melanoma, one murine melanoma, and a rat **glioblastoma**. Tumors were established by injection of tumor cells s.c. in nude and C57BI/6 mice, resp., and stereotactically into the brain of Sprague Dawley rats. Animals in the treated group were co-injected with packaging cells producing recombinant **retrovirus** carrying the HSV-tk gene, and followed by i.p. administration of GCV. In short term studies, we obsd. inhibition of tumor growth for all the tumor models evaluated ($p < 0.01$). In long term studies, using the C6 rat glioma line, 50% of the animals survived longer than 75 days ($p < 0.0001$), and were able to reject a contralateral challenge with C6 parental cells. Histol. and immunohistochem. anal. showed the presence of an inflammatory infiltrate composed by T lymphocytes, macrophages and polymorphonuclear cells. These data demonstrate that suicide genes might represent an attractive form of cancer gene therapy in the treatment of brain tumors and their intracerebral dissemination.

L4 ANSWER 55 OF 94 MEDLINE
ACCESSION NUMBER: 1998101689 MEDLINE
DOCUMENT NUMBER: 98101689 PubMed ID: 9440739
TITLE: Phase I trial of retroviral-mediated **transfer** of the human MDR1 gene as marrow chemoprotection in patients undergoing high-dose chemotherapy and autologous stem-cell transplantation.
AUTHOR: Hesdorffer C; Ayello J; Ward M; Kaubisch A; Vahdat L; Balmaceda C; Garrett T; Fetell M; Reiss R; Bank A; Antman K
CORPORATE SOURCE: Department of Medicine, College of Physicians and Surgeons of Columbia University, New York, NY, USA.. csh1@columbia.edu
CONTRACT NUMBER: P30-CA13696-21 (NCI)
R21 CA66244-01 (NCI)
UOI CA65838 (NCI)
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, (1998 Jan) 16 (1) 165-72. Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980206
Last Updated on STN: 19980206
Entered Medline: 19980127

AB PURPOSE: Normal bone marrow cells have little or no expression of the MDR p-glycoprotein product and, therefore, are particularly susceptible to killing by MDR-sensitive drugs, such as vinca alkaloids, anthracyclines, podophyllins, and paclitaxel and its congeners. Here we report the results of a phase I clinical trial that tested the safety and efficacy of **transfer** of the human multiple drug resistance (MDR1, MDR) gene into hematopoietic stem cells and progenitors in bone marrow as a means of providing resistance of these cells to the toxic effects of cancer chemotherapy. PATIENTS AND METHODS: Up to one third of the harvested cells of patients who were undergoing autologous bone marrow transplantation as part of a high-dose chemotherapy treatment for advanced cancer were **transduced** with an MDR cDNA-containing **retrovirus**; these **transduced** cells were reinfused together with unmanipulated cells after chemotherapy. RESULTS: High-level MDR **transduction** of

erythroid burst-forming unit (BFU-E) and colony-forming unit-granulocyte macrophage (CFU-GM) derived from **transduced** CD34+ cells was shown posttransduction and prereinfusion. However, only two of the five patients showed evidence of MDR **transduction** of their marrow at a low level at 10 weeks and 3 weeks, respectively, posttransplantation. The cytokine-stimulated **transduced** cells may be out-competed in repopulation by unmanipulated normal cells that are reinfused concomitantly. The MDR retroviral supernatant that was used was shown to be free of replication-competent **retrovirus** (RCR) before use, and all tests of patients' samples posttransplantation were negative for RCR. In addition, no adverse events with respect to marrow engraftment or other problems related to marrow transplantation were encountered. CONCLUSION: These results indicate the feasibility and safety of bone marrow gene therapy with a potentially therapeutic gene, the MDR gene.

L4 ANSWER 56 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 21
ACCESSION NUMBER: 1998:62012 CAPLUS
DOCUMENT NUMBER: 128:212789
TITLE: Restoration of growth arrest by p16INK4, p21WAF1, pRB, and p53 is dependent on the integrity of the endogenous cell-cycle control pathways in human **glioblastoma** cell lines
AUTHOR(S): Costanzi-Strauss, Eugenia; Strauss, Bryan E.; Naviaux, Robert K.; Haas, Martin
CORPORATE SOURCE: Cancer Center, University of California, San Diego, San Diego, CA, 92093-0063, USA
SOURCE: Experimental Cell Research (1998), 238(1), 51-62
CODEN: ECREAL; ISSN: 0014-4827
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of this study was to demonstrate that the induction of growth arrest in human **glioblastoma** multiforme (GBM) cell lines by **retrovirus**-mediated **transduction** of growth control genes was dependent upon the integrity of specific endogenous control pathways. The authors assessed the status of the endogenous p16INK4A, p21CIP1, pRb, or p53 genes in eight GBM lines. As expected, the authors found varied combinations of gene defects. The outcome of **transducing** five of these cell lines with p16INK4A, p21CIP1, pRb, or p53 genes was not entirely predictable. The growth-inhibitory effects mediated by the **transfer** of the gene encoding p16 was dependent on the presence of the pRb protein, but was independent of p53 status. P21, a broadly active CDK inhibitor and a strong inducer of growth arrest, was not a universal growth suppressor in the group of **glioblastoma** cell lines analyzed. The suppression of GBM cell proliferation by viruses encoding pRb or p53 was generally predictable and appeared to be independent of the status of either p16 or p21. Suppression of cell growth was assessed by a colony formation assay, by observance of alterations in morphol., and by cell viability staining for trypan blue exclusion. The authors findings suggest that to accomplish the suppression of GBM cell proliferation by the **transduction** of these cell-cycle control genes, the status of endogenous cell-cycle control genes must be taken into account.

L4 ANSWER 57 OF 94 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:285874 CAPLUS
DOCUMENT NUMBER: 127:351
TITLE: Functional expression of human p21WAF1/CIP1 gene in rat glioma cells suppresses tumor growth in vivo and induces radiosensitivity
AUTHOR(S): Hsiao, Michael; Tse, Victor; Carmel, Jason; Costanzi, Eugenia; Strauss, Bryan; Haas, Martin; Silverberg,

Gerald D.
CORPORATE SOURCE: Department of Neurosurgery, Stanford University Medical Center, Stanford, CA [redacted]4305, USA
SOURCE: Biochemical and Biophysical Research Communications (1997), 233(2), 329-335
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study reports the successful growth suppression of a rat **glioblastoma** model (RT-2) both in vitro and in vivo by the insertion of p21WAF1/CIP1, a neg. cell cycle regulatory gene, into the tumor cells. Greater than 95% of the tumor cells expressed p21 protein after being infected with pCL based p21 **retrovirus** at 4.times.M.O.I. (multiplicity of infection). The p21-infected cells showed a 91% redn. in colony forming efficiency and a 66% redn. in growth rate. More prominent p21 staining was found in cells exhibiting histol. evidence of senescence. Intracranial implantation of the infected cells showed complete disappearance of the p21-infected cells at day 10 and long-term survival of the animals compared to controls. Injection of pCLp21 virus into tumor established in situ showed tumor necrosis and gene expression. In a clonogenic radiation survival assay, a 93% redn. of surviving colonies of p21-infected cells was seen in comparison to vector-infected control cells and to p53-infected cells after exposure to 8 Gy (800 rads).

L4 ANSWER 58 OF 94 MEDLINE
ACCESSION NUMBER: 97377825 MEDLINE
DOCUMENT NUMBER: 97377825 PubMed ID: 9233425
TITLE: Gene therapy in brain tumours: implications of the size of **glioblastoma** on its curability.
AUTHOR: Izquierdo M; Cortes M L; Martin V; de Felipe P; Izquierdo J
M; Perez-Higueras A; Paz J F; Isla A; Blazquez M G
CORPORATE SOURCE: Departamento de Biologia Molecular/Centro de Biologia Molecular Severo Ochoa, Facultad de Ciencias, Universidad Autonoma de Madrid, Cantoblanco, Spain.
SOURCE: ACTA NEUROCHIRURGICA. SUPPLEMENTUM, (1997) 68 111-7.
Journal code: 0140560. ISSN: 0065-1419.
PUB. COUNTRY: Austria
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971013
Last Updated on STN: 19971013
Entered Medline: 19971001

AB The authors have used the thymidine kinase/ganciclovir system to block **glioblastoma** multiforme neoplastic cells in vivo, both in experimental animals and in two patients in which the more conventional therapies had been unsuccessful. In the Wistar rat it was found that the curability potential of the system is correlated with tumoral volume. Tumours smaller than 20 mm3 can be cured with defective **retrovirus** that do not carry the Herpes simplex thymidine kinase (Hsvtk) gene. While tumours smaller than 150 mm3 can regress totally by the kinase/ganciclovir system, those above that size cannot be cured by this treatment. In humans the situation seems very similar in that the authors have been unable either to reduce the tumour size of recurrent patients with tumour volumes larger than 100 cm2 applying the standard thymidine kinase/ganciclovir gene therapy or to prolong their survival time more than 8 months [7]. When a combination of size reduction by neurosurgery and gene therapy was

used the survival time increased considerably. Two patients have been treated by partial surgery and repeated treatment with thymidine kinase/ganciclovir through an Ommaya reservoir connected to a catheter leading into the tumour cavity. The magnetic resonance imaging (MRI) of these patients show only a residual tumoral growth along side the tumoral bed. The procedure may be partially controlling the proliferation of cancerous cells, because, these two patients having recurrent **glioblastoma**, are alive 11 and 17 months after the beginning of the treatment.

L4 ANSWER 59 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 22
ACCESSION NUMBER: 1996:433211 CAPLUS
DOCUMENT NUMBER: 125:106189
TITLE: The pCL vector system: rapid production of helper-free, high-titer, recombinant **retroviruses**
AUTHOR(S): Naviaux, Robert K.; Costanzi, Eugenia; Haas, Martin; Verma, Inder M.
CORPORATE SOURCE: Laboratory Genetics, Salk Institute, San Diego, CA, 92186, USA
SOURCE: Journal of Virology (1996), 70(8), 5701-5705
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We describe the construction and characterization of retroviral vectors and packaging plasmids that produce helper-free **retrovirus** with titers of 1 .times. 106 to 5 .times. 106 within 48 h. These vectors contain the immediate early region of the human cytomegalovirus enhancer-promoter fused to the Moloney murine leukemia virus long terminal repeat at the TATA box in the 5' U3 region, yielding the pCL promoter. By selecting vectors designed to express genes from one of four promoters (dihydrofolate reductase, Rous sarcoma virus, long terminal repeat, or cytomegalovirus), the pCL system permits the investigator to control the level of gene expression in target cells over a 100-fold range, while maintaining uniformly high titers of virus from transiently **transfected** producer cells. The pCL packaging plasmids lack a packaging signal (.DELTA..psi.) nd include an added safety modification that renders them self-inactivating through the deletion of the 3' U3 enhancer. Ecotropic, amphotropic (4070A), and amphotropic-mink cell focus-forming hybrid (10A1) envelope constructions have been prepd. and tested, permitting flexible selection of vector pseudotype in accordance with exptl. needs. Vector supernatants are free of helper virus and are of sufficiently high titer within 2 days of transient **transfection** in 293 cells to permit infection of more than 50% of randomly cycling target cells in culture. We demonstrated the efficacy of these vectors by using them to **transfer** three potent cell cycle control genes (the p16INK4A, p53, and Rb1 genes) into human **glioblastoma** cells.

L4 ANSWER 60 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 23
ACCESSION NUMBER: 1996:742784 CAPLUS
DOCUMENT NUMBER: 126:30060
TITLE: **Retrovirus**-mediated gene **transfer** of B7-1 and MHC class II converts a poorly immunogenic **neuroblastoma** into a highly immunogenic one
AUTHOR(S): Heuer, Josef G.; Tucker-McClung, Cheryl; Gonin, Rene; Hock, Randy A.
CORPORATE SOURCE: School Medicine, Indiana University, Indianapolis, IN, 46202, USA
SOURCE: Human Gene Therapy (1996), 7(17), 2059-2068

CODEN: HGTHE3; ISSN: 1043-0342
PUBLISHER: Liebert
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The T cell co-stimulatory mol. B7-1 was **transduced** into a poorly immunogenic murine **neuroblastoma** cell line (Neuro-2a, N-2a) alone or in combination with MHC class II genes to test the ability of these genes to stimulate antitumor immunity. N-2a cells **transduced** with B7-1 exhibited reduced tumorigenicity, whereas N-2a cells overexpressing both MHC class II (syngeneic, I-A.kappa.) and B7-1 totally abrogated tumorigenicity. Rejection of I-A.kappa./B7-1 cells was dependent on both CD4+ and CD8+ T cells. The ability of both vaccines to induce protection against parental N-2a was temporally dependent on the time of secondary N-2a challenge. To investigate the immunity generated by N-2a/B7-1 and N-2a/I-A.kappa./B7-1 vaccines, we tested the ability of these modified cells to stimulate in vitro the proliferation of syngeneic splenocytes from naive mice. A significant increase in splenocyte proliferation was obsd. with N-2a/I-A.kappa./B7-1 cells compared to N-2a cells. We also detd. that vaccination with N-2a/I-A.kappa./B7-1 cells was able to generate cytotoxic T cell responses to unmodified N-2a cells. The introduction of B7-1 and I-A.kappa. into N-2a was able to convert a poorly immunogenic tumor to a highly immunogenic one; however, mice bearing large established unmodified tumors had little response to vaccination with N-2a/I-A.kappa./B7-1 cells. Our results emphasize the importance of tumor immunogenicity in the treatment of established tumors with MHC class II/B7-1 tumor cell vaccines.

L4 ANSWER 61 OF 94 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:489656 BIOSIS
DOCUMENT NUMBER: PREV199699212012
TITLE: Treatment of C6 glioma by in situ **retrovirus transfer** of a "suicide" gene using an encapsulated packaging cell line.
AUTHOR(S): Padrun, V. (1); Martinet, O. (1); Schreyer, N. (1); Joseph, J. M. (1); Breakefield, X. O.; Aebischer, P. (1)
CORPORATE SOURCE: (1) Gene Therapy Cent., CHUV, Lausanne Univ., Lausanne Switzerland
SOURCE: Society for Neuroscience Abstracts, (1996) Vol. 22, No. 1-3, pp. 766.
Meeting Info.: 26th Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 16-21, 1996
ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 62 OF 94 MEDLINE
ACCESSION NUMBER: 96381785 MEDLINE
DOCUMENT NUMBER: 96381785 PubMed ID: 8789798
TITLE: Human malignant brain tumor response to herpes simplex thymidine kinase (HSVtk)/ganciclovir gene therapy.
AUTHOR: Izquierdo M; Martin V; de Felipe P; Izquierdo J M; Perez-Higueras A; Cortes M L; Paz J F; Isla A; Blazquez M G
CORPORATE SOURCE: Departamento de Biologia Molecular/Centro de Biologia Molecular Severo Ochoa, Facultad de Ciencias (modulo-C-X), Universidad Autonoma de Madrid, Spain.
SOURCE: GENE THERAPY, (1996 Jun) 3 (6) 491-5.

Journal code: 9421525. ISSN: 0969-7128.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961108

AB Growing cells from human brain tumors have been treated in vitro and in vivo with murine therapeutic retroviral producer cells. The therapeutic **retrovirus** carried the potential suicide gene thymidine kinase (tk) from the herpes simplex virus (HSV). After a few days, in which a large proportion of the tumoral cells had the opportunity to acquire a copy of the **retrovirus**, treatment with ganciclovir was initiated and considered responsible for considerable cell death both in vitro and in vivo. The in vivo experiments were performed in five adult patients who had failed standard therapy and were expected to survive only a few weeks.

L4 ANSWER 63 OF 94 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:256417 BIOSIS
DOCUMENT NUMBER: PREV199698812546
TITLE: Recombinant virus-mediated **transfer** of the wild-type p53 gene is a potent therapeutic strategy against various types of human cancer.
AUTHOR(S): Kagawa, S. (1); Fujiwara, T. (1); Ogawa, N. (1); Hamada, M. (1); Hizuta, A. (1); Tanaka, N. (1); Orita, K. (1); Cai, D. W.; Zhang, W.-W.; Roth, J. A.
CORPORATE SOURCE: (1) Okayama Univ. Med. Sch., Okayama Japan
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1996) Vol. 37, No. 0, pp. 339.
Meeting Info.: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 64 OF 94 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:684005 CAPLUS
DOCUMENT NUMBER: 126:6007
TITLE: Murine **neuroblastoma** vaccines produced by retroviral **transfer** of MHC class II genes
AUTHOR(S): Hock, Randy A.; Reynolds, Brian D.; Tucker-McClung, Cheryl L.; Heuer, Josef G.
CORPORATE SOURCE: Herman B Wells Center Pediatric Research, Indiana University School Medicine, Indianapolis, IN, 46202-5225, USA
SOURCE: Cancer Gene Therapy (1996), 3(5), 314-320
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Appleton & Lange
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Malignant tumors express tumor-related antigens, but effective antitumor immunity does not occur in the primary host. One hypothesis is that there is insufficient stimulation of T-cell responses due to ineffective antigen presentation. An approach to overcome these deficiencies is to modify

tumor cells to express major histocompatibility complex (MHC) class II genes and thus facilitate the presentation of antigens directly by tumor cells. Our expt. with a murine **neuroblastoma** cell line (neuro-2a) **transduced** with DR (xenogeneic), I-Ab (allogeneic), or I-Ak (syngeneic) MHC class II genes support this notion. The relative potencies of the modified neuro-2a to induce immunity to unmodified neuro-2a were neuro-2a/DR > neuro-2a/I-Ab > neuro-2a/I-Ak. Modified neuro-2a also could stimulate naive splenocyte proliferation in vitro. The relative magnitude of the proliferative responses seen after stimulation with modified tumor cells was neuro-2a/DR > neuro-2a/I-Ab > neuro-2a/I-Ak > unmodified neuro-2a. Hence, the tumor cell-induced splenocyte proliferative responses obsd. in vitro correlate with the effectiveness of the tumor cell vaccines to induce antitumor immunity in vivo. These data show that the expression of exogenous MHC class II on tumor cells is a potent stimulus for specific antitumor immunity. Because of the correlation of the in vivo and in vitro immune responses to modified tumor cells, the tumor-induced lymphocyte proliferation assay may be useful in evaluating tumor cell vaccines produced by addnl. genetic modifications of tumor cells.

L4 ANSWER 65 OF 94 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 24
ACCESSION NUMBER: 1996:279755 CAPLUS
DOCUMENT NUMBER: 125:27142
TITLE: Infection of human cells by murine ecotropic viruses: retroviral vectors carrying the hygromycin resistance-encoding gene
AUTHOR(S): Suzuki, Hiroshi; Brown, G. Dalon; Ohno, Kouichi; Meruelo, Daniel
CORPORATE SOURCE: Department of Pathology, Kaplan Cancer Center, New York University Medical Center, New York, NY, 10016, USA
SOURCE: Gene (1996), 170(2), 255-9
CODEN: GENED6; ISSN: 0378-1119
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The construction of a new retroviral vector, pSKV, is described. This vector carries 2 unique cloning sites, located between 2 Moloney leukemia virus-derived LTR, into which genes of interest may be introduced. The gene encoding hygromycin resistance (HyR) was subsequently introduced into one of the two sites, producing a second vector (pSKV/HyR) contg. a unique SfiI site for the introduction of cDNA clones under the control of the cytomegalovirus (CMV) promoter (P-CMV). The cDNA (mH13), encoding a protein that has been shown to serve as a murine ecotropic retroviral receptor in transient assays, was cloned into the SfiI site (pSKV/HyR/mH13). Both constructs can be packaged into retroviral particles following **transfection** into an appropriate packaging cell line. Stable **transfectants** of the human **glioblastoma** cell line (U118MG) carrying each of these 2 constructs were generated by **transfection** and subsequent Hy selection. Clones expressing both the selectable marker and the mH13 gene, but not those expressing only the selectable marker, are susceptible to infection with murine ecotropic retroviral particles. These cells (HyR and mH13 pos.) were then exposed to CRE/Xtk culture supernatant, a packaging cell line producing ecotropic retroviral particles carrying the HSV-TK (Herpes simplex virus-thymidine kinase) and neoR (neomycin-resistance) genes. Selection was in the presence of G418. In vitro growth of the U118MG/HyR/mH13/TK cells, but not that of the U118MG/HyR/mH13 cells, was inhibited by ganciclovir (GCV), indicating the successful **transfer** of HSV-TK by infection of human cells with